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EXAMINER	
KIM, TAEYOON	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,126	CONRAD, RICHARD C.	
	Examiner	Art Unit	
	Taeyoon Kim	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48 and 50-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48 and 50-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-48 and 50-72 are pending.

Election/Restrictions

Per the decision made on May 4, 2007 on a petition for reconsideration of restriction requirement, the Groups of I, III, IV and VI invention are rejoined with the previously elected Group II invention.

Claim 49 is cancelled, claims 58-72 are newly added, and Claims 1-48 and 50-72 have been considered on the merits.

Response to Amendment/Arguments

The claim rejection made to claim 45 under 35 U.S.C.§112 is withdrawn due to the amendment.

In the response to the previous office action mailed on Jan. 5, 2007, applicant argued that the 096' patent (Laugharn et al. US 6,111,096) fails to provide (a) one of skill in the art with an expectation of success and (b) motivation or suggestion to modify the cited references. This assertion was based on the argument that the '096 patent requires the use of hyperbaric or hydrostatic pressure (i.e. increased pressure), and in the absence of increased pressure one of skill in the art would have no expectation that the currently claimed method would successfully be used to isolate small RNAs. This argument is not persuasive to overcome the rejection. This is because the limitation of "the use of hyperbaric or hydrostatic pressure" taught by '096 patent is not required to render the current invention obvious as discussed in the previous rejection. Applicant argued that since the increased pressure is required for the success of the invention disclosed by Laugharn et al. and in the absence of such limitation, the invention of Laugharn et

al. would not be successful. This argument is nothing to do with the basis of the rejection made by the examiner in the previous office action. Since no such limitation is mentioned in the claimed invention, it is not necessary to consider such limitation in determining expected success of using the method of the reference. The requirement of increased pressure is required only for the invention made by Laugharn et al., but not by the instant invention. The additional references cited in the previous office action (i.e. RNA STAT-60™, Moss and Ambros) provide supporting evidence to Laugharn et al. to clarify the basis of the claim rejection, rather than supplementing missing limitation of Laugharn et al. Therefore, the claim rejection does not require motivation or suggestion because Laugharn et al. render all the limitation in the claimed invention obvious.

Applicant is advised that based upon the recent decision by the US Supreme Court in KSR v. Teleflex, Inc. (82 USPQ2d 1385, 2007), for establishing *prima facie* case of obviousness, it has been established that the TSM test (i.e. teach or suggest /motivation/reasonable expectation of success) is not considered as the only rationale to be used for claim rejection under 35 U.S.C.§103.

However, due to the rejoinder of previously withdrawn claims, the claim rejection made under 35 U.S.C.§103 based on Laugharn et al. is now withdrawn.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claims 50-53 and 57 disclose steps of using a first solid support and a second solid support for a sequential application of lysate/alcohol mixtures in steps (d) through (g). These steps are not supported by the specification. The specification does not disclose any of

these steps.

Claim Objections

Claims 11-13 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 11 is dependent on claim 10, which is dependent on claim 9, which is dependent on claim 8, which is dependent on claim 7, and claim 7 is dependent on claim 6. Thus, claim 11 comprises all the limitations listed in the claims 1 and 6-10. While claim 6 already discloses a limitation to the lysing solution comprising detergent, claim 11 discloses the same limitation of comprising detergent without further limiting. It appears that the limitation "detergent" in claim 6 is inadvertently added.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 14-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 and 14 disclose the concentration of the detergent or the buffer. However, it is not clear whether the concentration of detergent or buffer disclosed is being a starting concentration before mixing in the lysing solution or being a final concentration in the lysing solution. Clarification is required.

Claims 15-17 disclose additional step of extracting small RNA from the lysate using an

organic solvent. It is not clear whether or not this step is carried out after step (a) or (b) in the method of claim 1. Furthermore, it is not clear whether only small RNA being extracted from the lysate or nucleic acids present in the lysate is being extracted. If the step only extracts small RNA from the lysate, applicant requires providing written description, under 35 U.S.C.§112, first para., how to selectively extract small RNAs only from the lysate.

Claims 46 and 64 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is a step of obtaining a sample containing miRNA or small RNA. Without having a sample containing miRNA or small RNA, the method could not be enabling. Thus, having a sample containing miRNA or small RNA is critical for the method of claimed invention.

Furthermore, claim 64 omits additional step of lysis the sample if the sample being cells or tissues to release the nucleic acids from the cells, unless the sample being already lyzed cells or crude lysate of cells, etc., which does not require lysis step.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 5, 63 and 72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 4 and 5 disclose a yield of the purification step being at least about 20% or 50%. It is not clear how the percentage of yield can be obtained without knowing the starting amount of small RNAs present in the cells. However, the specification does not disclose how a person of ordinary skill in the art to determine the total small RNAs present in cells. Without knowing how to determine the total amount of small RNAs present in any cell utilized in the method of current invention, a person of ordinary skill in the art would not have obtained the yield of small RNAs obtainable from the method of the current invention.

Claims 63 and 72 disclose limitations to the method of claim 60 wherein the first wash solution comprising ethanol at 70%, and the second wash solution comprising ethanol at 80%. This limitation is not supported by the specification, therefore, introducing a new matter situation.

Claims 64-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a sample which does not require a lysis step (e.g. cell lysates), does not reasonably provide enablement for intact cells or tissues which require a lysis step to release nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Claim 64 discloses steps of isolating small RNA from ANY sample adding an ethanol solution at the concentration of 35% to 70%, applying the sample to a mineral support, eluting small RNA and using or characterizing the small RNA molecules. Unless the sample containing free floating small RNA, it is required to have a lysis step to release the nucleic acids including small RNAs present in any cells or tissues. Without this step, simply adding ethanol to ANY sample does not enable to isolate small RNAs from the sample. In addition, as pointed out in the

rejection under 35 U.S.C.§112, 2nd paragraph (see above), the sample has to contain small RNAs. Merely claiming ANY sample, which may or may not contain small RNAs, clearly does not enable the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-48 and 50-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over a manual for micro RNA isolation kit (Stratagene, 2000) (web.archive.org/web/20000823201150/http://www.stratagene.com/manuals/200344.pdf) in view of Bost et al. (US 6,111,096) in further view of Ekenberg et al. (US 6,218,531).

Claims 1-48 and 50-72 are drawn to a method of purifying small RNA (microRNA) comprising steps of lysis of cells using a lysing solution comprising a detergent or a chaotropic agent, precipitation of RNA with alcohol (ethanol), precipitation of proteins with guanidinium and/or phenol and chloroform, applying the lysate to a solid support, eluting small RNA from the support with low-ionic strength solution, collecting the eluted small RNA; a method for isolating miRNA or siRNA from cell lysates comprising a) obtaining a sample having miRNA or siRNA, b) adding an alcohol solution at about 35 to 70% to the sample, c) adding an extraction solution to the sample, d) applying the sample to a mineral or polymer support, and e) eluting the siRNA or miRNA from the support; a limitation to the eluted miRNA or siRNA being enriched at least about 10-fold by mass; a method of isolation small RNA comprising steps of lysing cells, adding

alcohol to the lysate, applying the lysate/alcohol mixture to a first solid support, collecting flow-through and adding alcohol to the flow-through and then applying to a second solid support, and eluting small RNA, wherein the alcohol concentration of the mixture applied to the first support being about 20% to 35% alcohol, wherein the alcohol concentration of the mixture applied to the second support being about 35% to 70% alcohol.

Stratagene manual teaches a method comprising steps of lysis of cells (see p.7) using a denaturing solution which contains 4 M guanidine isothiocyanate (guanidinium), 0.5% sarcosyl (N-lauroyl sarcosine) and 20 mM sodium acetate (buffer) (see p.21), extraction with phenol and chloroform (see p.8), adding isopropanol (alcohol) to the lysate.

Stratagene manual does not teach the use of solid support such as glass or silica material or eluting small RNA from the solid support.

Bost et al. teach the solid phase (solid support) such as glass or silica material in a form of bead (see paragraphs [0060] and [0065]) for RNA isolation, first wash solution containing chaotropic agent, guanidine thiocyanate (see Example 5), wash solution containing ethanol (see paragraph [0100], Example 5), and a step for eluting nucleic acids from the solid support with a low ionic strength solution containing 10 mM Tris at 56°C (see paragraph [0118], Example 5).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to use the solid support and washing steps of Bost et al. in the method of Stratagente manual because both methods are drawn to isolation of RNA, and the use of solid support in purification of nucleic acid is well known in the art, which provides convenience and higher purity in purification of nucleic acids. Thus, a person of ordinary skill in the art would have used the solid support and subsequent washing steps using washing solutions, and eluting

RNA bound to the solid support of Bost et al. in the method of Stratagene manual.

The US Federal Circuit has recently explicitly stated that in order to make a *prima facie* case of obviousness, the suggestion and motivation to combine said references need not be explicitly stated in the text of the references. Rather, consideration of common knowledge and common sense when combining references is not only permitted *but required.* See DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 80 USPQ2d 1641 (Fed. Cir. 2006) which states:

> ""Suggestion" test for obviousness does not require that suggestion, teaching, or motivation to combine cited prior art references be found in references themselves, or that such suggestion or motivation be explicitly stated; suggestion test is flexible rather than rigid and categorical, recognizing motivation to combine found in knowledge of persons of ordinary skill in art or nature of problem to be solved, as well as in references, and test not only permits, but requires, consideration of common knowledge and common sense."

In addition, the Supreme Court has recently stated that the suggestion and motivation to combine is not the only rationale to make the prima facie case of obviousness. See KSR v. Teleflex 82 USPQ2d at 1385, 2007.

Claim 20 discloses the step of adding alcohol in the lysate prior to extraction with an organic solvent. It would have been obvious for a person of ordinary skill in the art at the time of invention made to switch the order of steps.

M.P.E.P. § 2144 recites, "The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law...If the facts in a prior legal decision are sufficiently similar to those in an application under

examination, the examiner may use the rationale used by the court." In *In re Burhans, 154 F.2d 690, 69 USPQ 330* (CCPA 1946), the court found that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results. In *In re Gibson, 39 F.2d 975, 5 USPQ 230* (CCPA 1930), the court found that selection of any order of mixing ingredients is *prima facie* obvious.

Although Stratagene manual in view of Bost et al. do not particularly teach the washing solution containing guanidinium and alcohol (claims 23 and 60), it would have been obvious to a person of ordinary skill in the art to add guanidinium in the washing solution because it is well known in the art that guanidinium is added to inactivate RNase, which degrades RNA molecules, and protect RNAs from degradation. Thus, the addition of guanidinium in the washing solution would be considered to be beneficial to protect RNA molecules from degradation.

With regards to the limitation disclosed in claims 24 and 61, it would have been obvious to a person of ordinary skill in the art to have additional washing step to enhance the removal of unwanted materials bound to the silica material. Furthermore, Bost et al. teach multiple washing steps in isolating RNAs (see Example 5).

The limitation of claim 26 of eluting small RNA from the solid support at about 60°C to about 100°C is obvious over the disclosure of Stratagene manual (see p.5) as well as Bost et al. Bost et al. disclose a step of eluting nucleic acid with an elution buffer at 56°C. The manual teaches application of heat at 68°C to enhance solubilization of RNA. Therefore, a person of ordinary skill in the art would have recognized that higher temperature would enhance elution of nucleic acids (small RNA) bound to the solid support and applied heat at 68°C to enhance elution of small RNA from the solid support as taught by Stratagene manual in view of Bost et

al.

Bost et al. teach the step of using centrifugation (see paragraph [0118]) to collect the set of beads as disclosed in claim 31.

Although Stratagene in view of Bost et al. do not teach filtration or magnetic capture for the collection of the set of beads, Ekenberg et al. teach filtration using vacuum to collect silica support (see column 6, lines 16-17) and as an alternative to centrifugation. Furthermore, Ekenberg et al. teach silica matrix in the form of magnetic beads, indicating a capability of magnetic capturing of the beads (see column 5, lines 38-41). Thus, it would have been obvious to a person of ordinary skill in the art to substitute centrifugation with filtration or magnetic capture, since it is well known in the art that filtration or magnetic capturing is an alternative way to substitute centrifugation to collect beads.

Although Stratagene in view of Bost et al. do not particularly teach the use of glass fiber as a solid support, it is well known in the art that glass fiber is an art-recognized equivalent of silica material as taught by Ekenberg et al. (see column 4, lines 13-17). Thus, it would have been obvious to a person of ordinary skill in the art to substitute silica gel or matrix of Bost et al. with glass fiber of Ekenberg et al.

Although Stratagene in view of Bost et al. in further view of Ekenberg et al. are silent in isolating small RNA such as miRNA or siRNA, since the method of the references is similar, if not identical, to the claimed invention in isolation of RNAs, and it is expected that the purified RNAs would encompass small RNAs with less than 200 nucleotides. Furthermore, Bost et al. teach that the method of Bost et al. utilizing solid support would be able to isolate tRNA or fragmented nucleic acid, which is a disclosed species of small RNAs in the instant application

(see paragraph [0059]). Therefore, the initial method steps of Stratagene which is for isolation of total RNAs from the cells or tissues, including small RNAs, would be further purified by the use of a solid support of Bost et al., allowing isolation of small RNAs such as tRNAs. Therefore, the intended use of isolating small RNA of the claimed invention would be carried out by the method of Stratagene in view of Bost et al. in further view of Ekenberg et al. unless proven otherwise.

With regard to the limitation to the concentration of guanidine isocyanate (chaotropic salt) (i.e. 1.6 M) in claim 72, Ekenberg et al. teach the concentration of chaotropic salt being between about 1 M and 6 M, and the preferable chaotropic salt being guanidine thiocyanate (which is sometimes referred to as guanidine isocyanate) (see column 14, lines 17-20).

Although Stratagene in view of Bost et al. in further view of Ekenberg et al. do not particularly teach each and every specific concentration of alcohol (e.g. 35-70% in a lysate/alcohol mixture; or 80% ethanol in wash solution) or the fold enrichment (i.e. 10-fold) of miRNA or siRNA, it would have been obvious to a person of ordinary skill in the art to optimize the concentration of alcohol or fold enrichment because a person of ordinary skill in the art would have recognized those concentration as result-effective variables. As such, the variables would be routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by those references. Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 CCPA 1955) (Claimed

process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed atI a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the :references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made especially in the absence of evidence to the contrary.

With regard to the method steps (e) through (g) disclosed in claim 50, which requires applying the flow-through lysate/alcohol mixture collected from step (d), it would have obvious to a person of ordinary skill in the art to repeat the steps of applying flow-through from the first solid support by applying the flow-through to the second solid support not to loose unbound nucleic acids from the first reaction between the lysate and a solid support.

Therefore, the invention as a whole would have been prima facie obvious to a person of

ordinary skill at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taeyoon Kim whose telephone number is 571-272-9041. The examiner can normally be reached on 8:00 am - 4:30 pm ET (Mon-Fri).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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